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Combination of Ki67 Proliferation Index and CD10 in Prognosis of Patients with Follicular Lymphoma

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Abstract

Background &Objective: Markers such as Ki67 and CD10 play a role in the prognosis of follicular lymphoma (FL). However, the combined effect of these factors is still unclear. Our objective was to determine the combination of Ki67 and CD10 in the prognosis in patients with FL.

Method: Twenty-seven patients with FL were retrospectively analyzed. Based on immune histochemical staining for Ki67 and CD10 that was performed in biopsy lymph node, the patients were grouped according to the levels of the Ki67 proliferation index (PI) and the presence of CD10. Univariate and multivariate analysis was performed according to Ki67 proliferation index (PI) levels and CD10 presence.

Results: The ROC curve (receiver operating characteristic) found that the cut-off point of 60% for Ki67 was statistically significant in the difference in survival rates. Multivariate analysis suggested that Ki67>60%, CD10 negative was a truly independent prognostic factor for progression- free survival (PFS) (*P*= 0.045 HR=4.817;*P*=0.038 HR=5.195, respectively). There was a statistically significant difference between the groups: CD10 positive/Ki67≤60%, CD10 positive/Ki67>60%, CD10 negative/Ki67≤60%, and CD10 negative/Ki67>60% (*P*=0.007). Patients with positive CD10/Ki67≤60% had the best PFS. Patients with negative CD10 /Ki67>60% had the worst PFS.

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Conclusion: Ki67>60%, CD10 negative are truly independent adverse prognostic factors for PFS in FL. Patients with CD10 negative/Ki67>60% had worst PFS.

Keywords

Ki67 proliferation index; CD10; Follicular lymphoma; FL; Prognosis.

Introduction

Follicular lymphoma (FL) is an indolent lymphoma and is associated with a long survival time (OS). However, many patients relapse and have short progression- free survival (PFS) [1,2]. There are common prognostic systems: FLIPI (Follicular Lymphoma International Prognostic Index), FLIPI2, m7-FLIPI [1]. These systems used clinical factors, laboratory factors, and genes in combination to calculate the prognostic score. However, these prognostic systems have limitations, especially in the development of new therapeutic methods [1,3,4]. Therefore, more risk factors are still being studied; especially there are many studies that pay attention to the use of markers. They are necessary for diagnosis and have prognostic significance [5,6].

Ki67 is a marker of cell proliferation with the controversial effect on FL. There are not many studies that examine the role of Ki67 in slow-growing diseases such as FL. Kawaguchi Y, et al. showed that the patients with high expression of Ki67 seem to have had worse OS [7]. But Xue T, et al. showed that patients with a higher Ki67 index had better PFS [8].

CD10 is a cell membrane metallopeptidase that is widely distributed on neoplastic cells in FL. It can be considered as a surrogate marker for a slow-growing disease such as FL. The appearance of loss of CD10 expression can be seen as a signal of a transformation that progresses. Chen SW et al. showed that loss of CD10 expression was related to leukemia transformation [9]. Camacho FI et al. suggested that strong positive CD10 was a favorable factor OS, but did not show how it was strong positive [10]. Bilalovic N et al. suggested that CD10 positive patients would have a longer OS [11]. However, there are almost no studies showing that the combination of Ki67 and CD10 has an effect on FL. Our aim was to determine the combination of Ki67 and CD10 in the prognosis in the patient with FL.

Methods

Patients

This study was carried out in Bach Mai Hospital, Hanoi, Vietnam. Twenty-seven patients, from March 2016 to July 2021, with de novo FL were retrospectively analyzed in our study. All patients were diagnosed by examination of lymph node biopsies based on H.E staining and immunohistochemical staining for CD20, CD10, CD3, CD5, CD23, Bcl2, Bcl6, MUM1 and Ki67. The diagnosis was made according to the WHO 2008 classification of hematopoietic and lymphoid tumors [12,13]. The patients were treated with the R-CHOP protocol (rituximab- cyclophosphamide, doxorubicin, vincristine,

prednisolone) or the R-COP protocol (rituximab- cyclophosphamide, vincristine, prednisolone). The response to therapy was determined according to the criteria of the International Working Group (RECIL 2017) [14].

Definition

CD10 had been scored as 'positive' when at least 30% of the cells showed expression [15].

Statistics

The ROC curve (receiver operating characteristic) was performed separately for Ki67 level to gain a predictive value for OS. This found cut-off was applied for PFS to determine if there was statistically significant difference in survival rate. The patients were then grouped according to the newly found Ki67 PI cut-off value. The patients were also grouped according to the presence of CD10.

Independent-sample T tests were used to analyze differences in quantitative variables between the groups of patients. The χ^2 or Fisher's exact tests were used to analyze differences in qualitative variables between the groups of patients.

The Kaplan-Meier method was used to analyze OS and PFS.

Univariate analysis (using the log-rank test) and multivariate analysis (using the Cox proportional hazards method) with the Ki67 and CD10 variables were performed to determine prognostic factors for OS and PFS.

Results

Patients characteristics

Table 1 shows that there were no statistically significant differences in laboratory indices between the two groups (Ki67≤60% vs. Ki67>60%, CD10 positive vs. CD10 negative).

	Ki67	N	Mean	*P*	CD10	N	Mean	*P*
Age (years)	≤60%	23	58.3043	>0.05	positive	17	56.8235	>0.05
	>60%	4	64.5000		negative	10	63.3000	
Hemoglobin (g/L)	≤60%	23	130.5217	>0.05	positive	17	133.2941	>0.05
	>60%	4	136.5000		negative	10	128.2000	
Platelet (x10^9/L)	≤60%	23	227.4348	>0.05	positive	17	224.3529	>0.05
	>60%	4	322.0000		negative	10	270.5000	
WBC (x10^9/L)	≤60%	23	11.7087	>0.05	positive	17	12.7665	>0.05
	>60%	4	7.6875		negative	10	8.3020	
LDH (U/L)	≤60%	23	260.1739	>0.05	positive	17	271.5294	>0.05
	.60%	4	241.0000		negative	10	233.2000	
AST (U/L)	≤60%	23	26.0435	>0.05	positive	17	24.8824	>0.05
	>60%	4	23.0000		negative	10	26.8000	
ALT (U/L)	≤60%	23	24.0000	>0.05	positive	17	25.5294	>0.05

	>60%	4	22.7500		negative	10	20.9000	
Albumin (g/L)	≤60%	23	39.5739	>0.05	positive	17	40.7529	>0.05
	>60%	4	37.0250		negative	10	36.5500	
Bilirubin (µmol/L)	≤60%	23	8.0783	>0.05	positive	17	7.9765	>0.05
	.60%	4	6.4000		negative	10	7.5800	
Ure (mmol/L)	≤60%	23	5.7261	>0.05	positive	17	5.7118	>0.05
	>60%	4	4.9500		negative	10	5.4400	
Creatinin (mmol/L)	≤60%	23	62.2783	>0.05	positive	17	61.0824	>0.05
	>60%	4	59.7500		negative	10	63.3000	

Table 1: Patients characteristics according to Ki67 and CD10.

There were also no significant differences in clinical indices (FLIPI, bone marrow involvement, hepatosplenomegaly, B syndromes, high tumor burden, Ann Arbor stage) between the two groups (Ki67≤60% *vs.* Ki67>60%, CD10 positive *vs.* CD10 negative) (Table 2).

Clinical factors		**Ki67**		***P***	**CD10**		***P***
		Ki67≤60% (n=23)	**Ki67>60% (n=4)**		**CD10 positive (n=17)**	**CD10 negative (n=10)**	
Ann Arbor Stage	IIB	1	0	>0.05	1	0	>0.05
	IIIA	1	0		1	0	
	IIIB	14	4		9	9	
	IVB	7	0		6	1	
	Total	23	4		17	10	
Bone Marrow Involvement	No	18	4	>0.05	13	9	>0.05
	Yes	5	0		4	1	
	Total	23	4		17	10	
Hepatosplenomegaly	No	16	4	>0.05	12	8	>0.05
	Yes	7	0		5	2	
	Total	23	4		17	10	
B Syndrome	No	1	0	>0.05	1	0	>0.05
	Yes	22	4		16	10	
	Total	23	4		17	10	
High Tumor Burden	No	0	0	>0.05	0	0	>0.05
	Yes	23	4		17	10	
	Total	23	4		17	10	
FLIPI	Low	1	0	>0.05	1	0	>0.05
	Inter	6	2		5	3	
	High	16	2		11	7	
	Total	23	4		17	10	

Table 2: Clinicopathological profile of patients.

Ki67 and CD10 in survival times (OS and PFS)

The ROC curve found that the cut-off point of 60% for Ki67 was statistically significant in the difference in OS (AUC=0.98, sensitivity: 100%, specificity: 90%,*P*=0.026), (Figure1). This cut-off was applied for PFS and it was determined that there was statistically significant difference in survival rate. In univariate analysis, OS and PFS in the Ki67 PI>60% group had decreased statistically significantly for 5 years, OS and PFS in the CD10 negative group also had decreased statistically significantly for 5 years, (Table 3).

Multivariate analysis showed that the Ki67>60%, CD10 negative was a truly independent adverse prognostic factor for PFS (*P*= 0.045, 0.038; respectively) (Table 3).

Table 4 and Figure 2 show that there was a statistically significant difference in PFS between the groups: CD10 positive/Ki67≤60%, CD10 positive/Ki67>60%, CD10 negative/Ki67≤60% and CD10 negative/Ki67>60% (*P*=0.007). Patients with positive CD10/Ki67≤60% had the best PFS. Patients with negative CD10/Ki67>60% had the worst PFS.

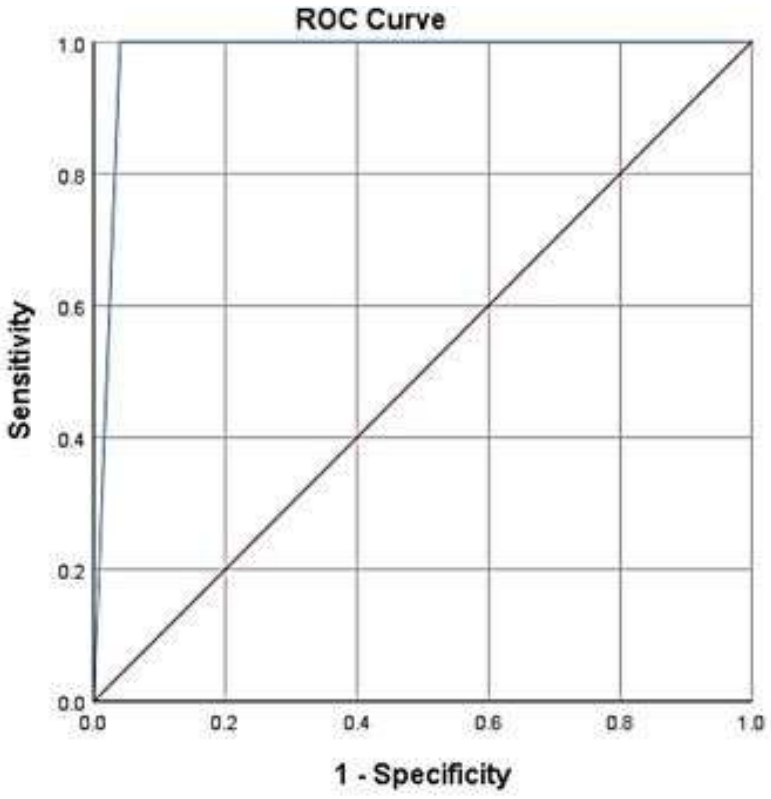

Figure 1: ROC (receiver operating characteristic) curve and area under curve for Ki67 percent (AUC=0.98, sensitivity: 100%, specificity: 90%, *P*=0.026).

Factor	Univariate analysis (OS)	Multivariate analysis (OS)		
	$P^{Log\text{-}rank}$ value	HR	95%CI	P^{Cox} value
Ki67				
≤60%	0.000			>0.05
>60%				
CD10				
Positive	0.049			>0.05
Negative				
Factor	**Univariate analysis (PFS)**	**Multivariate analysis (PFS)**		
	$P^{Log\text{-}rank}$ value	HR	95%CI	P^{Cox} value
Ki67				
≤60%	0.016	1		0.045
>60%		4.817	1.034-22.454	
CD10				
Positive	0.017	1		0.038
Negative		5.195	1.094-24.666	

Table 3: Univariate and multivariate analysis for survival times.

Factors	PFS (months)	*p*
CD10 positive/ Ki67≤60%	45.696	0.007
CD10 positive/ Ki67>60%	29.000	
CD10 negative /Ki67≤60%	27.729	
CD10 negative /Ki67>60%	3.333	

Table 4: Combination of Ki67 and CD10 in prognosis for progression free survival.

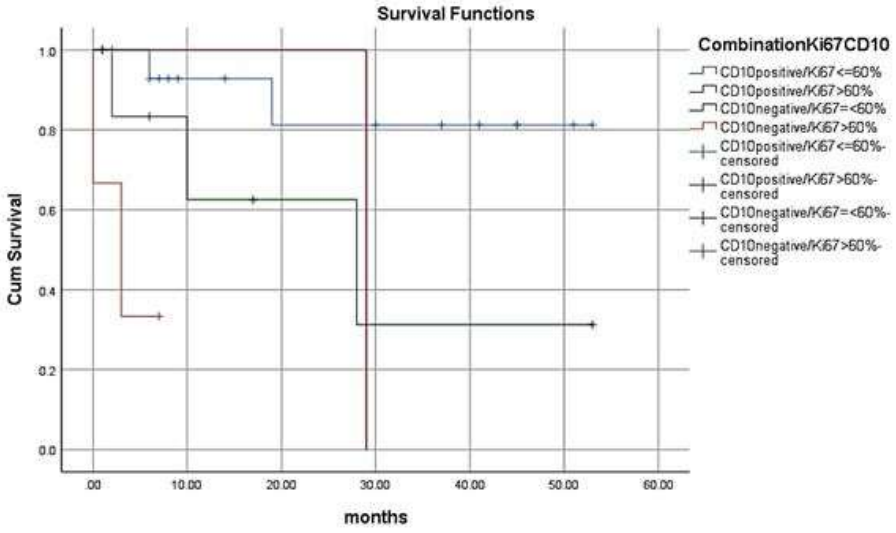

Figure 2: Progression free survival according to the combination of Ki67 and CD10.

Discussion

Unlike DLBCL (diffuse large B cell lymphoma) or MCL (mantle cell lymphoma) [16,17], the prognostic value of Ki67 in Fl is controversial. In some univariate analyzes, high expression of Ki67 appears to be a significant adverse factor, as in a study by Kawaguchi Y et al. or in a study by Xerri L et al. [7,18]. However, in multivariate analysis, these studies have not shown a statistically significant difference. Llanos M et al. also showed the same result [19]. Furthermore, Camacho FI et al. did not observe any differences in OS between patients who were grouped by Ki67 expression [10]. But Xue et al. showed the surprising conclusion that a higher Ki67 was a favorable factor for PFS [8]. In the univariate analysis, our study showed that at a high expression level (>60%), Ki67 has an adverse effect on OS and PFS. But in the multivariate analysis, high expression of Ki67 has only an adverse effect on PFS. Ki67 is a proliferation antigen, so it is generally an adverse factor in isolation. However, when expressed in a slow-growing disease such as FL and considered with other factors, the analysis becomes more difficult.

Unlike Ki67, the favorable role of CD10 in FL appears to be more consensual. In univariate and multivariate analysis, Camacho FI et al., Bilalovic N et al., both suggested that CD10 expression was related to significantly better OS [10,11]. However, when multivariate analysis was performed, our study showed that the CD10 negative was a truly independent adverse prognostic factor only for PFS, not for OS.

When evaluating the association between Ki67 and CD10 in the effect on survival time, our study showed that there was a statistically significant difference in PFS between the groups: CD10 positive/Ki67≤60%, CD10 positive/Ki67>60%, CD10 negative/Ki67≤60%, and CD10 negative/Ki67>60% (*P*=0.007). Patients with positive CD10/Ki67≤60% had the best PFS. Patients with negative CD10 /Ki67>60% had the worst PFS. In contrast, in multivariate analysis, Camacho FI, et al. suggested that

CD10 was a favorable factor for OS, while Ki67 was not significant [10]. However, this research was based on a group treated with a regimen without rituximab, while in our study, all patients were treated with a protocol containing rituximab. This result is completely consistent with the idea that, in the era of rituximab, PFS was used to assess the outcome of follicular lymphoma rather than OS.

Our study has some limitations, as there are patients with symptomatic disease or with a high tumor burden, who are indicated for chemotherapy. However, FL is an indolent lymphoma, so there is a not small number of patients without symptomatic disease or with low tumor burden, who are indicated for observation. Therefore, this study has not yet covered all patients with FL and should continue to be conducted with a large number of patients, with indications for chemotherapy and observational groups.

Conclusion

Ki67>60%, CD10 negative are truly independent adverse prognostic factors in FL for PFS. Patients with CD10 negative/Ki67>60% had worst PFS.

Ethics

The study protocol was approved by the Ethics Committee. The patient's consent was waived by the committee, as this study was a retrospective observational study.

Financial Disclosure Statement

No financial support was received for this study.

Conflicts of Interest/Funding

The authors declare no conflicts of interest.

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